Hill's Small Systems Nanothermodynamics: A Simple Macromolecular Partition Problem with a Statistical Perspective

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Abstract

Using a simple example of biological macromolecules which are partitioned between bulk solution and membrane, we investigate T.L. Hill's phenomenological nanothermodynamics for small systems. By introducing a *systems size dependent* equilibrium constant for the bulk-membrane partition, we obtain Hill's results on differential and integral chemical potentials μ and $\hat{\mu}$ from computations based on standard Gibbsian equilibrium statistical mechanics. It is shown that their difference can be understood from an equilibrium re-partitioning between bulk and membrane fractions upon a change in system's size; it is closely related to the system's fluctuations and inhomogeneity. These results provide a better understanding of the nanothermodynamics and clarify its logical relation with the theory of statistical mechanics.

1 Introduction

With great advances in material preparations at nanoscale in recent years, there is a growing interest in the thermodynamics of small systems [1, 2]. Nanothermodynamics, a phenomenological theory developed by T.L. Hill in the early 1960s for small equilibrium systems, has become one of the major formalisms for quantitative treatment of equilibrium nanoscale materials [3, 4]. There are many experimental and computational work that have verified the theory, see for examples [5, 6].

The greatest strength of thermodynamics, being absolute and abstract, is often its weakness: It usually provides no molecular mechanism and insights into chemical and biochemical processes. The same dichotomy applies to Hill's nanothermodynamics: The

key concept in the theory is a difference between *differential* and an *integral* froms of many non-extensive thermodynamic quantities due to smallness of a system. For example, since Gibbs free energy $G(N, p, T)$ is not linearly proportional to the systems size N, $\mu = \partial G/\partial N$ and $\hat{\mu} = G/N$ are different. The difference is intuitively understood: It is due to contributions such as surface effect.

In biophysical chemistry, biological macromolecules are often treated as having discrete conformational states, and interaction with ligands as stoichiometric binding. While this approach is only an approximation, it often provides much more powerful intuitive understanding of the physical processes that underly molecular thermodynamics. A case in point is J.A. Schellman's theory of three-component system with mixed solvents [7]. While a thorough treatment of this problem involves perferential interaction coefficients, discrete stoichiometric binding model has provided greater intuition [8].[1]

The fundamental premises of a *small system* is that its thermodynamic properties are not strictly proportional to the system's size [4]. A system's size, however, can be represented by several different quantities: The number of molecules N in a system; the volume V of a system, or the total energy E of a system. In chemistry and biochemistry, concentration $x = N/V$ is a widely used intensive quantity. We shall refer to system's size in term of its volume in the rest of the paper. In terms of V, the Helmholtz free energy F of a three-dimensional small system could have the form

$$F = Vf(x, T) + a(x, T)V^{2/3} + b(x, T) \ln V + \cdots , \tag{1}$$

where the term in $V^{2/3}$ is associated with a surface energy.

In the present work, we first consider the following simple problem: N non-interactive macromolecule M are in a system which consists of bulk solution and membrane. (One could think of a vesicle with lipid membrane.) Each M molecule has three discrete conformational states: 0, 1 in the bulk and 2 on the membrane. We assume the equilibrium constant between states 0 and 1 is K_1 and between states 0 and 2 is K_2. $K_1 = p_1/p_0$ and $K_2 = p_2/p_0$ where p_i is the probability of an M being in state i in equilibrium. K_1 is independent of amount of membrane in the system; but K_2 is critically dependent on the ratio of membrane surface S to bulk volume V, thus the system's size. Assuming simple geometry with surface to volume ratio $S/V = V^{-1/3}$ and homogeneity in both bulk and

[1] A difference between differential and integral forms of macromolecular interaction also appears in the theory of binding: Thermodynamic binding can go to zero while molecular interaction is the strongest [9].

membrane phases, it is reasonable to assume that $K_2(V) \propto V^{-1/3}$. Thus the equilibrium partition function for a single M molecule, with the state 0 as the refererence state:

$$Z_1 = 1 + K_1 + K_2(V) \to 1 + K_1 \tag{2}$$

in the limit of $V \to \infty$. The simple example can be easily generalized to more general macromolecular partition problem, and a key formula relating μ and $\hat{\mu}$ first appeared in [4], will be derived.

A few remarks on Eq. (2) are in order: (i) Z_1 looks like a binding polynomial, but it is actually independent of the concentration of the M. This is because we have assumed that the$N$ macromolecules are non-interactive. Hence, Z_1 is the "partition function" of a single M molecule. The partition function for the whole system is $Z_N = Z_1^N$.

(ii) $K_2(V) = p_2/p_0$ as a function of V is itself a complex problem in general. For our simple model, we shall completely neglect surface free energy of the membrane. Furthermore, if one treats macromolecule-membrane association as simple Langmuir absorption, with $N(p_0 + p_1)/V$ and Np_2/S being the concentrations of the M in bulk and on membrane. Then one obtains $p_2/(p_0 + p_1) \propto S/V$. Since $(p_0 + p_1) = (1 + K_1)p_0$, one has $p_2/p_0 \propto S/V \sim V^{-1/3}$. For the present analysis, the key is that $K_2(V)$ is a function of V. The result in Eq. (6) given below does not depend on a specific functional form of $K_2(V)$.

The novel idea of the present work is to introduce the *systems size dependent* equilibrium constant(s), (i.e., more generally potential of mean force or conditional free energy). It is shown that if one starts with a mechanistic based statistical approach, following Gibbs, to small systems, then the small systems nanothermodynamics naturally emerges.

One of the salient features of Hill's nanothermodynamics is its *ensemble dependence*: When a systems boundary becomes significant, how a statistical thermodynamic system is maintained at the boundary matters. In the past, dependence upon details of an ensemble at its boundary leads to the phenomenon of *entropy-enthalpy compensation* [10, 11], which can be understood from relaxing certain internal constraints. In Sec. 3.1 we show that this perspective is also fruitful in understanding the difference between differential and integral chemical potentials μ and $\hat{\mu}$.

2 Bulk-Membrane Partition: A Simple Example

We now consider a simple system in which there are N non-interactive macromolecle M. Each M has three distinct states: states 0 and 1 are in bulk solution and state 2 is associated with membrane. It is clear that the ratio between total membrane to total bulk volume is a function of the systems size V: Thus by simple geometric consideration $K_2(V)$ is volume dependent. The partition function for the small system with constant pressure p and temperature T is:

$$Z(N,p,T) = (1 + K_1 + K_2(V))^N \,, \tag{3}$$

in which $V = V(N,p,T)$ is a function of N.[2] Therefore,

$$G(N,p,T) = -k_B T \ln Z(N,p,T), \tag{4}$$

$$\hat{\mu}(N,p,T) = \frac{G(N,p,T)}{N} = -k_B T \ln\left(1 + K_1 + K_2\right), \tag{5}$$

$$\mu(N,p,T) = \frac{\partial G(N,p,T)}{\partial N} = \hat{\mu} - \frac{k_B T K_2 \left(\frac{\partial \ln K_2}{\partial \ln N}\right)_{p,T}}{1 + K_1 + K_2}, \tag{6}$$

where $\hat{\mu}$ and μ are integral and differential chemcial potentials introduced by Hill [4]. In the last term of Eq. (6), $(\partial \ln K_2 / \partial \ln N)$ is an intensive quantity, $K_2 \propto V^{-1/3}$ and $1 + K_1 + K_2 \to 1 + K_1$. Hence it is on the order of $K^{-1/3}$. Thus, μ and $\hat{\mu}$ are the same for a macroscopic system when $G(N,p,T)$ asymptotically becomes an "extensive" quantity: $G \propto N$.

Eq. (6) can be easily generalized into

$$\mu(N,p,T) - \hat{\mu}(N,p,T) = \left\langle \left(\frac{\partial \mu_i^o(N,p,T)}{\partial \ln N}\right)_{p,T} \right\rangle = \left(\frac{\partial \hat{\mu}(N,p,T)}{\partial \ln N}\right)_{p,T}, \tag{7}$$

where

$$\mu_i^o(N,p.T) = -k_B T \ln K_i(N,p,T) \tag{8}$$

and the average $\langle \cdots \rangle$ is performed with respect to $i = 0, 1, 2$. Eq. (7) clearly shows why and how the small systems thermodynamics depends on the nature of ensemble; and why the difference μ and $\hat{\mu}$ will be ensemble specific. Eq. (7) agrees with what obtained by Hill ([4], Part I, p. 30, Eq. 2-12):

$$\mu - \hat{\mu} = \left(\frac{\partial \hat{\mu}}{\partial \ln N}\right)_{p,T}. \tag{9}$$

[2] Mathematically more rigorous, one needs to solve the problem with self-consistency among Eqs. (3), (4) and: $V(N,p,T) = (\partial G / \partial p)_{N,T}$.

3 Thermodynamic Hierarchy and Nanothermodynamics

3.1 Perturbation and relaxation in thermodynamic systems

The chemical potential μ is the increment in free energy of a system when its number of molecules increased by 1 [12]. Therefore, it can be considered as a *perturbation* to the thermodynamic system. The idea advanced in [10], originally proposed by A. Ben-Naim [13], is to view the response of a thermodynamic system to a perturbation as two parts:

(i) Constraining the distribution among all the populations un-changed, what is the increase in free energy of the system due to the perturbation?

(ii) Inevitably, however, the perturbation will cause a shift (i.e., re-distribution, re-partitioning) in the equilibrium among the populations. There is an additional free energy change associated with this re-organization process.

This perturbation-relaxation view of thermodynamics of complex systems yielded a possible explanation for the so-called "entropy-enthalpy compensation" phenomena [13, 10, 11]: Note that the chemical potentials for all the subcomponents, μ_j, of an equilibrium system have to be the same. Thus, the free energy change associated with (ii) is essentially zero if the perturbation is infinitesimal. In contrast, the corresponding entropy and enthalpy of the subcomponents, s_j and h_j ($h_j - Ts_j = \mu_j$), can be very different. Thus, a large contributions to entropy and enthalpy from the process in (ii) are expected.[3]

Applying the same idea to thermodynamics of our simple example, a perturbation leads to a shift in equilibrium between the "bulk" and "membrane" fractions. More specifically, introducing an additional M molecule causes a change in the system's volume V under isobaric (i.e., constant p) condition. This change in V is global: It causes the change of K_2 for each and every molecule M in the system.

3.2 Spatial inhomogeneity

"Size" is a geometric concept. The unique feature of nanothermodynamics of small systems is *spatial inhomogeneity* that partitions the particles in a system into different populations whose proportions scale differently with systems size. In Hill's theory, this partition is

[3]Both steps in this gedankenexperiment are carried out under an isothermal condition. They can not be realized in a laboratory. They are different from the adiabatic (isoentropic) and isothermal processes in the derivation of the fundamental equation of thermodynamics.

implicit: cluster growth naturally leads "surface" and "interior"; in our simple model this partition is explicitly assumed: states 0 and 1 versus 2.

With this geometry in mind, there will be two answers to the following question: What is the change in system's free energy if one introduces one additional particle into the system? Accordingly, answer (i) assumes that the proprotion is unchanged; and answer (ii) assumes there is a shift in equilibrium distributions between different populations.

The answer (i) is precisely the macroscopic result, $\hat{\mu}$. It is intimately related to the free-energy perturbation theory [14, 15]:

$$\Delta G^o(A \to B) = -k_B T \ln \left\langle \exp\left(-\frac{E_B - E_A}{k_B T}\right) \right\rangle_A, \tag{10}$$

in which the average is carried out in terms of the equilibrium distribution of the unperturbed system. Note that Eq. (10) assumes that the phase space, over which the ensemble average $\langle \cdots \rangle_A$ is carried out, is the same before and after the perturbation.

The answer (ii) however, contains exactly a contribution from small systems effect: The addition of a particle changes the size of the system, thus the phase space, on the order of $1/N$. This change causes a shift in the equilibrium between "surface population" to "bulk poplulation", which affects all N particles in the system. This is given in Eq. (7).

Realizing the difference between these two answers led Hill to introduce dN_t and $d\mathcal{N}$. The former corresponds to a change in the total number of particles, thus gives μ (answer ii); the latter changes the number of particles but keeps the equilibrium population proportion by "adding an independent copy of the small system", thus gives $\hat{\mu}$ (answer i).

3.3 Rapidly stirred biochemical reaction systems

For a small biochemical reaction system which is rapidly stirred, the theory of Delbrück-Gillespie process [16, 17], with its probability distribution given by the chemical master equation and its trajectories follow Gillespie algorithm, predicts that its stationary probability distribution, in the limit of large size, has the generic form

$$f(x) \propto \exp\left(-V\phi(x)\right), \tag{11}$$

where x is the concentration of biochemical species, V is system's volume, and $\phi(x)$ is a function of only intensive quantities. Applying Laplace's method for integrals [18, 19], this

result leads to the conclusion that for a rapidly stirred system without geometric inhomogeneity, the partition function

$$\begin{aligned} Q(V,\mu,T) &= V\int dx\; e^{-V\phi(x)} \\ &\approx Ve^{-V\phi(x^*)}\int dx\; e^{-\frac{V}{2}\phi''(x^*)(x-x^*)^2} \\ &= e^{-V\phi(x^*)}\sqrt{\frac{2\pi V}{\phi''\left(x^*\right)}}, \end{aligned} \tag{12}$$

where $x^*(\mu)$ is the macroscopic concentration. Therefore,

$$-k_BT\ln Q(V,\mu,T) = k_BTV\phi(x^*) + O(\ln V), \tag{13}$$

where $O(\cdots)$ is the mathematical symbol called Bachmann-Landau notation. It stands for "on the order of $\cdots$". Eq. (13) should be compared with Eq. (3): $-k_BT\ln Z(N,p,T) = -k_BTVx^*\ln(1+K_1)+O\left(V^{2/3}\right)$ where $x^* = N/V$. For rapidly stirred nanoscale systems, the correction to the extensive term is on the order of logarithm of an extensive quantity: $\ln V$ or $\ln N$. When there is a spatial partitioning, e.g., compartimentalization, however, terms on the order of fractional power of the extensive quantity arise. For system with bulk-membrane partition, this term is on the order of $V^{2/3}$.

A biological cell is a small thermodynamic system. Applying the present result to a collection of cells, one realizes that there are two macroscopic limits: (a) Classical biochemistry studies cell extracts with membrane removed; (b) permeable cells that preserve the ratio between membrane surface area to bulk volume. They correspond precisely the two ensembles of Hill's.

3.4 Kinetics of re-partitioning

All the above discussion has been exclusively on equilibrium thermodynamics. We suspect there is in fact a kinetic aspect of the thermodynamics of small systems. Nonequilibrium thermodynamics for heterogeneous systems and for nanoscale systems have become matural subjects in recent years [20, 21, 22]. If one takes a kinetic perspective of the response of a small system upon perturbation [10], one sees that the conformation re-partitioning between the bulk and surface could indeed be observed kinetically. This connection between thermodynamics and kinetics deserves further investigation [23, 24, 25].

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